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Primary Gastrointestinal Lymphoma in Kuwait. An 11-yr Retrospective Analysis of 108 Cases

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Abstract—*One hundred and eight cases of primary gastrointestinal lymphoma from the files of Kuwait Cancer Control Centre over a period of* 11 yr *were analysed retrospectively. The occurrence was* 47 *in the proximal small intestine,* 38 *in the stomach,* 18 *in the distal ileum and five in the colon and rectum. The majority of the patients were in stage III. Using a modified Rappaport's classification, lymphocytic lymphoma was the commonest histologic type* (60%) *as compared to histiocytic lymphoma* (19%). *Four patients had early IPSID (immunoproliferative small intestinal disease). The 'Western' type of lymphoma occurred in the fourth decade while the 'Mediterranean' type occurred in the third decade of life. The latter occurred more commonly among people of low socioeconomic background. Chemotherapy was the single most effective mode of treatment. Addition of surgery, radiotherpy or both did not improve the* 2-yr *survival but did improve the* 5-yr *survival.*

INTRODUCTION

PRIMARY lymphoma of the gastro-intestinal (GI) tract is considered to be rare, representing approximately 1-2% of GI malignancies [1]. In our area we see GI lymphomas more commonly than in the West (18% of all GI malignancies according to the Kuwait Cancer Registry). To review our experience we undertook a retrospective analysis of the cases that were entered in the files of the Kuwait Cancer Control Centre (KCCC) from 1971 to 1981. This centre serves the whole population of Kuwait and patients referred from the neighbouring Arab countries. The population of Kuwait rose from about 800,000 in 1971 to 1.36 million by 1981 [2]. The ratio of Kuwaitis to non-Kuwaiti Arabs in this period was approximately 1:1, with a predominance of males in the latter.

MATERIALS AND METHODS

All 112 cases of primary GI lymphomas in the KCCC during the period 1971-1981 were reviewed by two gastroenterologists and two oncologists. As in other recent reports [1, 3], lesions were considered primary to the GI tract if the initial symptoms and predominant lesions were confined to the stomach, small bowel or large bowel. In accordance with the criteria proposed by Dawson *et al.* [4], there were no palpable superficial nodes or roentgenographic evidence of mediastinal disease, the peripheral blood smear revealed no leukaemic or lymphomatous abnormalities, and at laparotomy all intra-abdominal lymphadenopathies corresponded to accepted lymphatic drainage routes which represent a secondary spread from the primary tumour. The histological sections from 103 cases were available and reviewed by two histopathologists. Two cases were re-classified as carcinomas and rejected from the study. A further two were excluded because of lack of adequate histological evidence of lymphoma. Nine patients were diagnosed elsewhere and slides were not available for review, but these cases were included since the diagnosis were made at reputable institutions. Thus a total of 108 cases were finally included in the study and their data were then analysed.

Patients were staged using primarily physical findings, operative notes and pathology. Other studies such as fibroptic endoscopy, radiology, lymphangiograms, isotopic and CT Scans, bone marrow biopsies and liver biopsies contributed information to staging. Eighty-four patients had

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undergone operation of which 50 had laparotomy and resection and 34 had laparotomy and biopsies (eight of these also had a bypass of an obstructive lesion). Of the remaining 24 patients 13 were staged using other available information. Eleven patients could not be staged. The cases were classified as stage I if the tumour was confined to the GI tract, stage II if there was spread to the local lymph nodes, stage III if the tumour extended beyond the local lymph nodes and stage IV if there were distant metastases. This classification is similar to those proposed by Lim *et al.* [5] and Nagui *et al.* [6].

The pathological material consisted of endoscopic biopsies (24), biopsies at laparotomy (34) and resected specimens (50). Haematoxylin and eosin-stained slides were obtained from the file in every case. In a selected number of cases PAS, reticulin and MGP stains were examined. Tests for detection of alpha heavy chain or facilities for immunoperoxidase staining were not available. The cases were classified using both a modified Rappaport classification as well as the working formulation [7], but it was expanded to include the IPSID group [8] (Table 1).

The treatment used depended on the general condition of the patient, the clinical stage of the disease and the tolerance of the patient to the modality of treatment. The general policy was to treat the patients with three courses of cyclophosphamide, oncovin and prednisone (COP) followed by total abdominal irradiation, aiming at 35 Gy in 6 weeks. The liver was shielded after 15 Gy and the kidneys after 20 Gy. The left kidney was not shielded anteriorly in patients with stomach involvement. This was followed by nine courses of COP in stages I–III. Patients with stage IV disease were treated by chemotherapy, aiming at 24 courses at least.

Life table analysis was used to compute survival rates. The survival rate was calculated from the time of diagnosis to the last follow-up or death.

The term 'Mediterranean' type was used if there was diffuse involvement of the upper small intestine, and 'Western' type was used to group the other lymphomas (localised type involving stomach, distal ileum, colon and rectum) in this study.

RESULTS

A total of 108 cases were analysed. Their age ranged from 3 to 76 yr, the mean age being 32 yr ('Mediterranean' type, 27.7 yr; 'Western' type, 36.3 yr). Nineteen patients were under the age of

Table 1. *Histological classification of lymphoma-modified Rappaport classification (with working formulation in parentheses)*

Histological type	Stomach ±duodenum	Distal ileum	Colon rectum	Duodenum, jejunum prox. ileum	Total
Histiocytic lymphoma—diffuse (malignant lymphoma large cell, immunoblastic)	6	2	1	11	20
Poorly differentiated, lymphocytic (malignant lymphoma, diffuse, small cleaved cells)	11	4	1	5	21
Intermediate differentiated, lymphocytic	4 27	1 9	1 3	2 25	8 64
Well-differentiated, lymphocytic (malignant lymphoma, small lymphocytic)	3	1	1	1	35
With plasmocytoid features	9	3		17	
Mixed histiocytic and lymphocytic, diffuse (malignant lymphoma, diffuse mixed small and large cells)	1			1	2
IPSID stage A				4	4
Burkitt's lymphoma (malignant lymphoma, small non-cleaved cells)		4		3	7
Hodgkin's disease				1	1
Unclassified	1				1
Total	35	15	4	45	99

15 yr. There were 75 male and 33 female patients in this study. The nationality distribution (the 'Western' type and the 'Mediterranean' type respectively in parentheses) is as follows: Kuwaitis, 32 (22 and 10); non-Kuwaiti Arabs, 65 (34 and 31); non-Kuwaiti non-Arabs, 11 (5 and 6). The stomach with or without the duodenum was involved in 38 patients (four were in stage I, 12 in stage II, 13 in stage III, four in stage IV and five were unstaged). The upper small intestine was involved in 47 cases (five were in stage I, 12 in stage II, 15 in stage III, nine in stage IV and six were unstaged). In 18 patients the involvement was in the distal ileum (two were in stage I, four in stage II, eight in stage III and four in stage IV). The rectum and/or colon was involved in five cases (four were in stage III and one was in stage IV). The commonest site was the upper small intestine (47), followed by the stomach (38). Majority of our patients were in stage III when first diagnosed (40 cases). Abdominal pain was the commonest symptom, occurring in 91 patients. Diarrhoea was present in only 10% of the 'Western' type but in 43% of the 'Mediterranean' type of lymphoma. None of the patients were asymptomatic.

The histological types of lymphoma in our series are shown in Table 1. Lymphocytic lymphoma was seen in 64 cases (60%) whereas histiocytic lymphoma was in only 20 cases (19%). We had four cases of stage A IPSID. These showed subtotal villous atrophy of the mucosa with crypt sparcity but normal surface epithelium. There was diffuse infiltration of plasma cells as well as lymphoplasmacytic cells confined to the lamina propria of the mucosa, but these showed no histological features of malignancy. Twenty-nine cases resulted from malignant transformation of early IPSID in the form of histiocytic lymphoma (11 cases) and well-differentiated lymphocytic lymphoma (18 cases). The former showed predominance of immunoblasts while the latter showed areas of diffuse lymphoplasmacytic infiltration extending through the whole thickness of the bowel in addition to the presence of scattered atypical immunoblastic cells.

Eighty-four patients had surgery, of whom 50 had resection and eight had bypass of an obstruction, and seven died postoperatively (operative mortality, 8.3%). Chemotherapy was the commonest mode of therapy used, and the commonest combination was COP. Eighty-two patients received chemotherapy. Radiotherapy in the form of total abdominal irradiation was used in 63 patients. Twelve patients received doses less than 20 Gy. In two patients with advanced disease no specific treatment was advised due to their very poor general condition. In one patient with early IPSID tetracycline was used as a single mode of therapy.

Figure 1 shows the overall survival rates for 108 cases. Forty-three patients (34%) survived less than 6 months. The actuarial 5-yr survival rate was 34% (29% for those under 15 yr of age and 35% for those above). Figure 2 shows the survival according to stage. Patients in stage I had an actuarial 5-yr survival of 86%, compared to 33% for stage II, 29% for stage III and 23% for stage IV. The differences between stage I and the other stages are statistically significant ($P < 0.05$).

The 5-yr survival according to various sites of involvement were analysed and are as follows: stomach 38%, distal ileum 43%, colon and rectum 20%, and proximal small intestine 29%. However, there was no statistically significant difference between these results. Figure 3 compares the survival of patients who were histologically classified as histiocytic lymphoma (HL) (20 cases), lymphocytic lymphoma—well differentiated (LWL) (35 cases) and lymphocytic lymphoma—poorly differentiated (LPL) (21

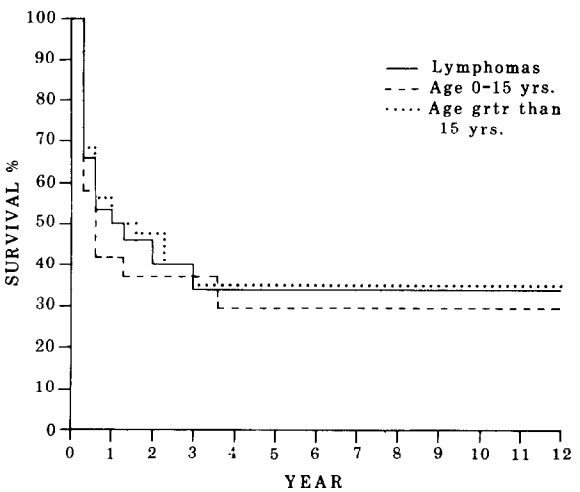

Fig. 1. Overall survival.

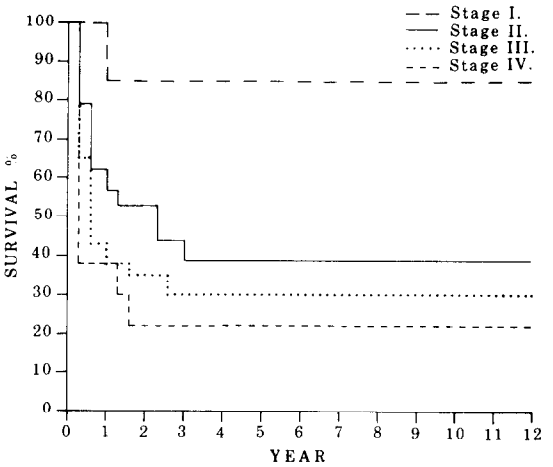

Fig. 2. Survival according to stage.

cases). There is a statistically significant difference in the 2-yr and 5-yr survival rates between LWL and LPL but not between LWL and HL or LPL and HL. Figure 4 shows the survival according to various modalities of treatment.

DISCUSSION

Primary GI lymphoma is relatively uncommon in the West (approximately 1-2% of all GI malignancies). In Kuwait lymphomas are more commonly seen. It accounts for 18% of all GI malignancies, 21% of all lymphomas and 33% of non-Hodgkin's lymphoma (Kuwait Cancer Registry). There has been a number of reports from the Middle-Eastern Arab countries which dealt with 'Mediterranean' type of lymphoma in general [9, 10]. In our study of 108 cases, we analysed both the 'Western' and the 'Mediterranean' types.

We had 47 (43%) cases of lymphoma involving the upper small intestine, 38 cases (35%) of the stomach and 18 cases (17%) of the distal ileum. In contrast, in the Western reports the usual site of involvement of lymphoma is the stomach, followed by small intestine—mainly the terminal ileum [11-14]. This disparity is probably due to the fact that IPSIDs are more common in our area and they characteristically involve the upper small intestine. The majority of these cases may, therefore, be the malignant transformation of early IPSID.

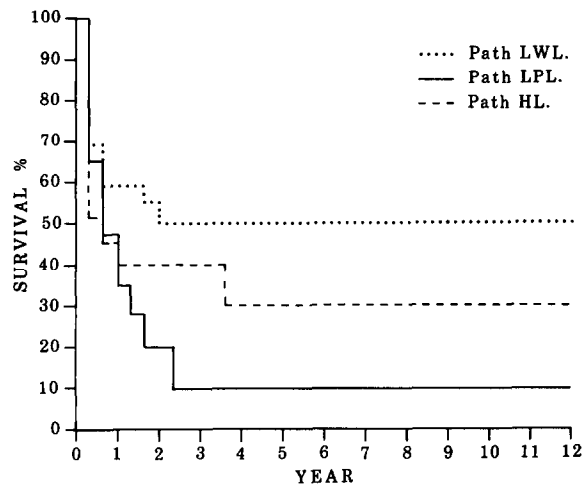

Fig. 3. Survival according to pathology.

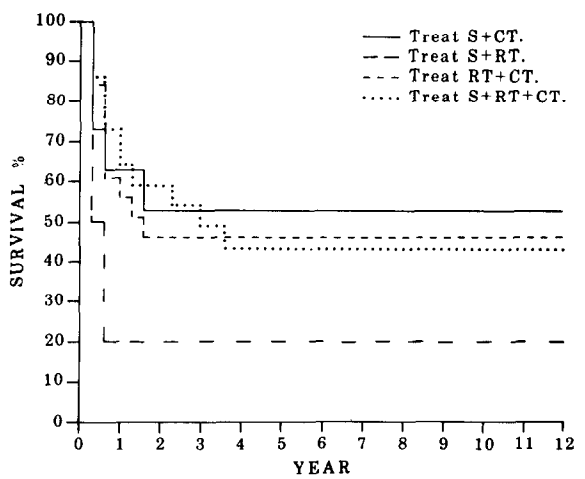

Fig. 4. Survival according to treatment.

The mean age of onset of lymphoma is about the third decade in our patients with 'Mediterranean' type, which is similar to other reports. However, it is interesting that the mean age of onset in our 'Western' type was the fourth decade, which is one decade younger than in most reported series [11, 15, 16]. This may be partly due to the younger age of our population as a whole.

Although the population ratio of Kuwaitis to non-Kuwaiti Arabs is 1:1, the number of cases of lymphoma among the non-Kuwaiti Arabs was twice that of the Kuwaitis (65:32). The difference in the frequency of the 'Mediterranean' type was more marked between the two populations (31 in non-Kuwaiti Arabs, compared to ten in Kuwaitis), while the difference was less obvious in the 'Western' type (34 and 22 respectively). This may be due to the fact that IPSID is known to be more prevalent among people of low socioeconomic background [14, 16].

The Kuwaitis in general have higher socioeconomic standards than the majority of non-Kuwaiti Arabs living in Kuwait. The predominance of males among the non-Kuwaiti Arab population may be another explanation.

The modified staging classification used in our study was an important determinant in our series. Stage I patients had the best prognosis when compared to the others. This is consistent with other reports in which a similar staging was used [3, 13]. Early IPSID cases did well initially (2-yr survival, 83%), but the 5-yr survival was only 21%. We had a significantly lower number of patients in stage I (seven cases) than in other reports [1, 12, 13]. Most of our patients were in a late stage (stage III = 40, stage IV = 18) when first diagnosed. This may be because many of our patients seek medical advice late. Another explanation is that infectious diarrhoea is more common in this area and it may mask the clinical picture of lymphoma in the initial stages.

In Kuwait lymphocytic lymphoma was more frequently seen (60%) than histiocytic lymphoma (19%), whereas the opposite is true in most reported series [3, 12]. Well-differentiated lymphocytic lymphomas formed the majority of our cases. It is interesting to note that a diffuse rather than nodular pattern was a histological feature seen in all our resected specimens.

We had only four cases of early IPSID, but we found that during this same period the pathology register had 37 cases of early IPSID entered in it. This discrepancy is due to the fact that until very recently early IPSID cases were not included in the KCCC file. These cases are being studied and will be reported in the near future.

Chemotherapy either alone or in combination with surgery and/or radiotherapy was the single most effective modality of treatment in this series. Thus chemotherapy when used alone produced a 2-yr survival of 48%, and there was no significant improvement when surgery, radiotherapy or both was added to it. However, the 5-yr survival was increased when radiotherapy, surgery or both was added to chemotherapy. However, these results were statistically not significant. Radiotherapy or surgery when used alone produced dismal results.

Although the majority of our cases were in a more advanced stage than in other reports, our data showed comparable 2- and 5-yr survival rates for all sites [11, 13]. This may be because many of our patients were in the group of histologically well-differentiated lymphocytic lymphoma, which has the best prognosis, and this brought our survival status to comparable levels.

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REFERENCES

1. Contreary K, Nance FC, Becker WF. Primary lymphoma of the gastrointestinal tract. *Ann Surg* 1980, **191**, 593-598.
2. *Kuwait Census 1980*. Kuwait, Ministry of Planning, 1982.
3. Weingrad DN, Decosse JJ, Sherlock P *et al.* Primary gastrointestinal lymphoma. A 30 year review. *Cancer* 1982, **49**, 1258-1265.
4. Dawson IMP, Cornes JS and Morson BC. Primary malignant lymphoid tumours of the intestinal tract. *Br J Surg* 1961, **49**, 80-89.
5. Lim FE, Hartman AS, Jan EGC *et al.* Factors in the prognosis of gastric lymphoma. *Cancer* 1977, **39**, 1713-1720.
6. Naqui MS, Burrows L, Hark AE. Lymphoma of the gastrointestinal tract. *Ann Surg* 1969, **170**, 221-231.
7. National Cancer Institute Working Formulation. *Cancer* 1982, **49**, 2112-2135.
8. *WHO Report in Alpha-chain Disease Meeting*. Geneva, WHO Publications, 1975.
9. Salem PA, Nasser VH, Shahid MJ *et al.* Mediterranean abdominal lymphoma or immunoproliferative small intestinal disease. *Cancer* 1977, **40**, 2941-2947.
10. Al Saleem T, Al Bahrani A. Malignant lymphoma of the small intestine in Iraq. *Cancer* 1973, **31**, 291-294.
11. Brady LW, Asbell SO. Malignant lymphoma of the gastrointestinal tract—Erskine memorial lecture 1979. *Radiolgy* 1980, **137**, 291-298.
12. Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract—a study of 117 cases presenting with gastrointestinal diseases. *Cancer* 1978, **42**, 693-707.
13. Green JA, Dawson AA, Lessells AM *et al.* Prognostic factors in gastrointestinal lymphoma. *Clin Oncol* 1981, **7**, 115-121.
14. Gray GM, Rosenburg SA, Cooper AD *et al.* Lymphomas involving the gastrointestinal tract. *Gastroenterology* 1982, **82**, 143-152.
15. Kalser MH. *Secondary Malabsorption Syndrome in Gastroenterology*. Bockus HL, ed. Philadelphia, PA, W.B. Saunders, 1976, 306-343.
16. WHO Memorandum. Alpha-chain disease and related small intestinal lymphoma. *Bull WHO* 1976, **54**, 615-624.